

Extremity Soft Tissue Sarcoma With Metastases to Abdominopelvic Surfaces

DANILO ZANARINI, MD, AND PAUL H. SUGARBAKER, MD, FACS*

Washington Cancer Institute, Washington Hospital Center, Washington, DC

Background: In a majority of patients with extremity soft tissue sarcoma, the lungs are the first site at which recurrent disease is detected. Other common sites of recurrence are the resection site, bone metastasis, and liver metastasis. Although abdomino-pelvic sarcomatosis is common as a site of recurrence for visceral and retroperitoneal sarcoma, it has not been previously reported for extremity sarcoma.

Method: We present three patients in whom extremity soft tissue sarcoma metastasized to the peritoneal surfaces, and in all three patients this was symptomatically the dominant site for recurrence. All of them underwent a palliative surgical cytoreduction and were then treated with intraperitoneal chemotherapy.

Results: In two of the three patients, isolated progression of peritoneal sarcomatosis has again occurred; one patient remains disease free at 14 months.

Conclusions: Metastasis to peritoneal surfaces within the abdomen and pelvis must be considered a possible site for systemic dissemination of extremity soft tissue sarcomas. Effective treatments for sarcoma spread to peritoneal surfaces would benefit this small but symptomatic group of patients. *J. Surg. Oncol.* 64:68–73 © 1997 Wiley-Liss, Inc.

KEY WORDS: extremity sarcoma; sarcomatosis; intraperitoneal chemotherapy; cytoreductive surgery; metastases

INTRODUCTION

Sarcomas are a diverse group of malignant tumors arising from tissues derived from the primitive mesoderm. The primary tumor may occur within a great variety of organs and tissues, thus accounting for the anatomic and histologic diversity of these tumors. [1] As a result of this diversity, the presenting symptoms and signs of sarcomas may be nonspecific, and the diagnosis is often delayed. Nevertheless, at the time of diagnosis the majority of patients do not have detectable distant metastasis. Initial therapy is directed at definitive treatment of the primary lesion, with a multimodality approach using surgery, chemotherapy, and radiation therapy [2,3]. With extremity soft tissue sarcoma, improved treatment of the primary lesion has resulted in a decrease of the local recurrence rate to <5% [4,5].

With improved local control, the mortality for this disease is largely attributed to the well-recognized propensity of soft tissue extremity sarcomas for hematogenous dissemination. The major site for recurrence is the lung.

Abdominopelvic sarcomatosis has been reported in approximately one-third of patients with retroperitoneal sarcomas, but it has been said not to occur when the primary sarcoma is in other sites [5].

We observed peritoneal sarcomatosis in three patients who had previously had an extremity soft tissue sarcoma. The peritoneal surface disease was histologically identical to that which had previously been definitively treated on the lower extremity. Also, no primary sarcoma within the abdomen or the pelvis was detectable. We concluded that extremity sarcoma can show a similar pattern of dissemination as does breast cancer and melanoma, with hematogenous metastasis to peritoneal surfaces.

Danilo Zanarini, M.D., is now at Clinica Chirurgica III, Osp. S. Orsola, via Massarenti 9, 40138 Bologna, Italy.

*Correspondence to: Washington Cancer Institute, 110 Irving Street, NW, Washington DC 20010.

Accepted 19 April 1996

The aim of this study is to describe three patients with peritoneal surface metastasis of extremity soft tissue sarcoma. This is an unusual and previously undescribed part of the natural history of this disease.

MATERIALS AND METHODS

Thirty-nine patients with abdominal or pelvic sarcomatosis have been treated for recurrent cancer between 1989 and 1995. In six of these patients, the primary site for the sarcoma was the small bowel or stomach and in 30 the primary tumor was in the retroperitoneum or abdominal wall. Three patients, all of whom had extensive sarcomatosis on abdominal and pelvic surfaces, had the primary tumor in the lower extremity. The complete medical histories on these patients were obtained and their pathology reports were reviewed, both from the primary tumor and from the disease resected from the abdomen and pelvis. All three patients underwent cytoreduction of the sarcomatosis from the abdomen and pelvis, so that generous tissue sampling was possible. Other sites of disease recorded in these patients were also noted. The pattern of distribution of the sarcoma to abdominal and pelvic surfaces was specially noted and was prospectively recorded at the time of cytoreductive surgery.

Patient 1

A 23-year-old woman was treated at another institution for an 8 cm diameter sarcoma on her anterior left thigh. The primary tumor mass was just above the knee and within the vastus medialis of the quadriceps muscle. This was treated with wide excision and interstitial radiation therapy. Histologic study showed a high-grade lipoblastic liposarcoma. Throughout her course no local recurrence developed. One year later, follow-up revealed metastatic sarcoma in the lung parenchyma. This was removed surgically and no further pulmonary disease occurred. After an additional 8 months, she was found to have a tumor in the left ovary with peritoneal seeding for which she underwent an oophorectomy. The histological report showed metastatic high-grade lipoblastic liposarcoma.

One year later she was referred to this institution for treatment of tumor masses in the left upper quadrant, in the right abdominal gutter, and in the lower portion of the left abdominal gutter extending into the pelvis. Cytoreduction included a right colectomy, a left colectomy, a pelvic peritonectomy, hysterectomy, omentectomy, and a right and left upper quadrant peritonectomy. Intraperitoneal doxorubicin and cisplatin were used as chemotherapy for the first 5 postoperative days. She died of progressive intra-abdominal and pelvic disease 3 months later.

Patient 2

A 45-year-old man was referred with a massive progression of sarcoma within the abdomen and pelvis. In

1988, he presented with a myxoid liposarcoma of his right anterior thigh and was treated with wide excision and radiation therapy. He had no local recurrence throughout his course. Approximately 3 years later, he developed another soft tissue tumor in the abdomen and in the chest. A second primary sarcoma was suspected, and he underwent resections of sarcomas in both the abdomen and the chest. In both instances, the pathologies were identical to that of the primary tumor and a second primary intra-abdominal tumor mass was not found.

Upon presentation to this institution 3 years later, he had continuous pain and a tensely distended abdomen. The patient was becoming increasingly debilitated as a result of several large intra-abdominal tumor masses, and he was beginning to show signs of intestinal obstruction. Palliative resection of massive myxoid liposarcoma was performed. At operation, multiple discrete tumor masses filled the pelvis and nearly all of the abdomen. Cytoreductive surgery with resection of rectosigmoid and descending colon, pelvic peritonectomy, and greater omentectomy was accomplished with minimal residual disease. Heated intraoperative intraperitoneal chemotherapy with cisplatin and early postoperative intraperitoneal chemotherapy with doxorubicin were utilized. The patient is alive 34 months later with progressive disease around the right common iliac vessels.

Patient 3

A 44-year-old man was referred because of a recurrent sarcoma within the abdominal cavity. In 1989, he underwent a wide excision of a sarcoma in the right popliteal fossa followed by local radiation using brachytherapy. The pathology showed a myxoid liposarcoma of intermediate grade.

After a 4-year disease-free interval, he developed a recurrence in the pelvis; the sarcoma deposit was described as filling the cul de sac of Douglas. The pathology was identical to that of the primary myxoid liposarcoma. No dominant tumor mass that could be identified as a second primary tumor was noted. He underwent a resection of the sarcoma nodules, but after 9 months he developed recurrences in the abdominal cavity and in the mediastinum, both of which were resected. The mediastinal site was irradiated using external beam and has shown no further evidence of disease.

One year later, a third resection of recurrent myxoid liposarcoma in the pelvis was performed, plus resection of multiple tumors on the small bowel mesentery and parietal peritoneum. Just 5 months later, sarcoma recurrence in all abdominal quadrants was seen on CT scan. The patient was referred to our institution, and an extensive cytoreduction cleared all visible evidence of sarcoma from the abdominal incision, right retrohepatic space, small bowel mesentery, and pelvis. Heated intraoperative intraperitoneal cisplatin and early postopera-

TABLE I. Clinical Features of Three Patients With Extremity Sarcoma That Resulted in Peritoneal Sarcomatosis

Patient Age, sex	Sarcoma type	Grade	Stage	Extremity involved	Clinical presentation of sarcomatosis	Disease-free interval	Other sites	Therapy	Status follow-up ^a
1 26 F	Round cell lipoblastic liposarcoma	High	IIIB	Left antero-lateral thigh	Bleeding and intestinal obstruction	8 months	Lung	cytoreduction + early postoperative intraperitoneal cisplatin and doxorubicin	DOD 3 m.
2 45 M	Myxoid liposarcoma	Low	IIB	Right anterior thigh	Debilitating abdominal distention, pain	3 years	Lung	cytoreduction + heated intraoperative cisplatin + early postoperative doxorubicin	AWD 19 m.
3 44 M	Myxoid liposarcoma	Intermediate	IIB	Right popliteal fossa	Pressure on bladder and dysuria	4 years	Mediastinum	cytoreduction + heated intraoperative cisplatin + early postoperative doxorubicin	NED 14 m.

^a DOD = dead of disease, AWD = alive with disease, NED = no evidence of disease.

tive intraperitoneal doxorubicin were used in an attempt to prevent a fifth recurrence of sarcomatosis. All specimens from six sarcoma resections showed an intermediate grade of myxoid liposarcoma identical to that of the primary tumor. At the time of writing, the patient was alive with no evidence of disease, 14 months after the last treatment.

RESULTS

The clinical features of these three patients are summarized in Table I. In all patients, treatment of the primary tumor was by surgical excision and local radiation therapy. Two of the three patients had brachytherapy. None of these patients had adjuvant systemic chemotherapy for treatment of the primary sarcoma. No patient developed recurrence in the extremity from which the primary sarcoma was resected.

The intervals between surgery for the primary tumor and treatment of sarcomatosis were 8 months, 3 years, and 4 years. All patients had prior abdominal and pelvic sarcoma resections before referral to the Washington Cancer Institute, but no second primary tumor mass was recognized. Two patients had a recurrence in the lung and another in the mediastinum. All patients underwent successful surgical resections of lung or mediastinal sarcoma metastasis without further disease recurrence at these sites.

At the Washington Cancer Institute, all patients underwent an extensive surgical cytoreduction. All the patients had large tumor masses at multiple sites within the abdominal cavity. The locations of the sarcoma deposits were carefully recorded in all three patients. The pelvic

peritoneum was most consistently involved in these patients, but the abdominal surfaces were also involved. No visceral or parietal peritoneal surfaces within the abdomen or pelvis was spared sarcoma involvement when all three patients are considered together.

No hepatic metastases or retroperitoneal or pelvic lymph nodes metastasis were found at the time of the cytoreductions or were recorded at other abdominal procedures.

The histological type of sarcoma for patient #2 and #3 (Table I) was myxoid liposarcoma. These two patients had a less fulminant progression of the disease with a longer disease-free interval between the treatment of the primary tumor and the diagnosis of the first recurrence. Patient #1 (Table I) had a round cell lipoblastic liposarcoma. In this patient the progression of the disease was much faster. Neither the histologic type nor the grade of the tumor changed during the course of the disease for all three patients.

DISCUSSION

We describe the clinical course of three patients who had definitive local treatment of an extremity soft tissue sarcoma, in that there was no local recurrence throughout the follow-up period. However, they developed extensive deposits of sarcoma on the peritoneal surfaces of the abdomen and the pelvis. In all three patients, the peritoneal sarcomatosis was the major site of metastases from the perspective of the patient's symptomatology. In these patients, other sites of sarcoma dissemination were controlled with surgery alone or surgery in combination with radiation therapy and chemotherapy. In all three of these

patients, the histologic type of the intraperitoneal tumor was identical to that observed in the extremity. Also, no other primary sarcoma within the abdomen or pelvis was discovered at any time during the patient's course. Our conclusion is that extremity sarcoma can metastasize hematogenously to peritoneal surfaces and cause peritoneal sarcomatosis.

It is possible that these patients had multiple primary sarcomas of the same histologic type occurring in the extremity, occurring extensively on peritoneal surfaces, and occurring in the thorax. But metastases from the extremity sarcoma to the thorax and to peritoneal surfaces seem to be more likely, since multiple primary sarcomas at many different anatomic sites with identical histological type have never been reported.

It is also possible that an occult primary sarcoma in the abdomen resulted in metastases to the lower extremity and to the chest. The long disease-free intervals between the diagnosis of the primary sarcoma and the sarcomatosis (8 months, 3 years, and 4 years) make this unlikely. An undetected and rapidly growing primary tumor in the abdomen or pelvis for such a long time period seems impossible. Moreover, in our three patients, sarcoma deposits in the abdomen and pelvis were multiple and widely distributed rather than large and solitary as would be expected with a primary intra-abdominal sarcoma. Finally, metastases from a primary sarcoma in the abdomen or pelvis to the extremity has not been previously reported [6].

The mechanism of dissemination of sarcoma from the lower extremity to the peritoneal surface is, most likely, by a hematogenous route. No route for direct extension of sarcoma cells to the peritoneal surface from the lower extremity is known to exist.

It is possible for peritoneal seeding to be associated with retroperitoneal lymph node metastases. The sarcoma could spread directly into the peritoneal cavity starting from the lymph nodes. But lymphatic dissemination is unlikely in our three patients because no lymph nodes in and around the abdomen or pelvis were found to be involved by malignancy, either by CT scan or by direct inspection at the time of cytoreductive surgery. Lymphatic metastasis are uncommon and occur in <5% of sarcoma patients [7,8]. The low rate of lymph node metastases observed for sarcomas occurs as a result of the limited lymphatic supply for mesodermal structures probably due to the unusual involvement of these tissues in a host defense against invasion by pathogens [9]. In a review of 374 patients referred to the National Cancer Institute, (Bethesda, MD) over a 24-year period, only three patients (2.6%) of 113 who had lymph nodes evaluated had evidence of metastasis [7]. Mazon and Suit [8] reported an incidence of lymph node involvement of 5.9% for 323 patients with stage M0 soft tissue sarcoma. There was <2% involvement in patients with low grade

sarcomas and 12% for those with high grade malignancies [8].

This pattern of dissemination to peritoneal surfaces is not unique to extremity sarcoma. Other tumors reported to cause peritoneal surface metastases are carcinoma of the breast and malignant melanoma. Dixon and colleagues [10] reported that infiltrating lobular carcinoma of the breast resulted in peritoneal carcinomatosis in 18% of patients with metastases. Also, infiltrating ductal carcinoma of the breast caused carcinomatosis in 1% of patients [10]. In an autopsy study Lamovec and Bracko [11] found peritoneal metastases in 60% of patients with infiltrating lobular carcinoma of the breast, and in 15.4% of patients with infiltrating ductal carcinoma. De la Monte and colleagues [12] reported that 33% of patients with melanoma will at some time in their course develop metastases to the peritoneal surfaces of abdomen and pelvis. The pattern of cancer dissemination recognized for breast cancer and malignant melanoma was similar to that seen in these patients with extremity soft tissue sarcoma.

Our postulate that the dissemination from extremity sarcoma to peritoneal surfaces was by the hematogenous route is supported by recent data that suggest that cancer cells are present in the bone marrow and at other hematogenous sites in a large number of patients with cancer [13–15]. These data are available because immunohistochemistry can identify a small number of cancer cells within normal tissue such as bone marrow, liver, or mesothelial cells from within the peritoneal space. From a clinical perspective, hematogenous dissemination becomes important only as these systemically distributed cancer cells adhere, implant, and then progress at a particular anatomic site. The sites for development of these metastases may be random; however, a predilection for the development of metastases may depend on the quantity of tumor cells at a particular anatomic site, on the receptors on both tumor cells and endothelial cells at these sites, and the likelihood of endothelial trauma.

Unfortunately, immunohistochemical markers for sarcomas are not available as they are for epithelial tumors. It is unlikely that small numbers of sarcoma cells in peritoneal fluid would be identifiable using immunocytochemical techniques that are currently available. But one may think of sarcoma as a systemic disease, as with epithelial malignancies.

In this model one would expect that a few patients with the systemic distribution of sarcoma cells would eventually develop sarcomatosis. In light of this hypothesis, the development of sarcomatosis from an extremity sarcoma may not be so surprising.

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COMMENTARY

This manuscript reports an unusual manifestation of metastatic sarcoma, that of peritoneal sarcomatosis. The first two patients developed pulmonary metastases prior to intraperitoneal metastases and could, therefore, have had their metastases metastasize. Disseminated disease after initial pulmonary metastases is not uncommon; there is no clinical or experimental evidence that aggressive treatment in this circumstance is effective.

Appropriate management of peritoneal sarcomatosis remains to be determined, but it is unlikely that the type of resection described in this article represents a realistic approach. As with any tumor that is incurable, the first consideration should be toward palliation of the patient's symptoms: bleeding, perforation, obstruction, or intractable pain should be treated to allow the patient to live as symptom-free as possible.

The next consideration should be treatment of the cancer itself. Palliation and definitive treatment may be one and the same, but not when multiple sites are involved with metastatic cancer (sarcoma). Zanarini and Sugar-

baker describe an aggressive debulking procedure followed by intraperitoneal chemotherapy. This is neither a logical nor a realistic approach when knowledge of tumor cell biology and the usual course of these tumor is taken into account. The first patient, with a high grade tumor, lived only 3 months. The next two patients, with low grade tumors, have followed the expected course for such patients, and there is no evidence that resection followed by intraperitoneal chemotherapy has altered the course of their cancers. Did chemotherapy add anything to surgery? Did surgery add anything to chemotherapy? These questions cannot be answered from this paper. The morbidity of this approach has not been discussed, nor has the quality of life issue been addressed. Therefore, these cases cannot be considered successes or models for care of such patients.

What, then, should be the approach to patients with sarcomatosis? Outside of a clinical trial, palliation of specific symptoms should be initially attempted. Systemic chemotherapy would be the mainstay of treatment; with a significant response, subsequent surgery to remove any gross residual disease or to relieve specific mechanical problems could be considered.

James P. Neifeld, MD

RESPONSE

From the perspective of cancer treatment, the comments by Dr. Neifeld must be carefully considered because his concepts regarding the management of metastatic cancer reflect the conservative, general surgical attitudes towards patients with disseminated disease. However, the success that has been achieved with the resection of metastases from extremity sarcoma, needs to be cautiously evaluated and not rejected outright because it does not fit "traditional practice guidelines" [1].

There is a conceptual basis to support the management of these extremity sarcoma patients who developed sarcomatosis. They all had a surgical complete response to clinically evident disease. No sarcoma deposit that could be demonstrated by a meticulous radiologic work-up and by painstaking exploration of the abdomen and pelvis was left behind. These patients were made disease free by surgery. In our judgement, physically fit patients that can be given a surgical complete response will have longer and better quality lives. This principle should guide all surgeons contemplating surgical procedures for recurrent or metastatic cancer.

In these three patients, the dominant clinical feature of sarcoma dissemination was the sarcomatosis. With disease controlled at all other sites, we successfully palliated all three of these patients with extensive disease on abdominal and pelvic surfaces. This was done with a combination of cytoreductive surgery and intraperitoneal chemotherapy. One of the patients did die 3 months later of progressive intra-abdominal disease. Another patient

remains alive and well at 10 months. The third patient remains alive with disease at 28 months following cytoreductive surgery and intraperitoneal chemotherapy.

Dr. Neifeld's comments regarding the components of these treatments are well taken. Is it the cytoreductive surgery that may cause temporary arrest of disease in these patients? Is it the intraperitoneal chemotherapy? At this point in time, our suggestion is that both treatments are necessary. One component of treatment removes all visible tumor deposits on the peritoneal surfaces; the other eliminates sarcoma cells that would eventuate in recurrence of the disease [2,3].

Of course, these three patients represent only a small fraction of sarcoma patients who develop sarcomatosis. We have treated a much larger number of patients with sarcomatosis from visceral sarcomas and from retroperitoneal sarcomas. Very often in the treatment of these diseases, or prior to the surgical intervention, sarcoma cells are disseminated on peritoneal surfaces [4]. They then become recurrent very shortly after resection of the primary tumor [5].

For these patients, combinations of intraperitoneal and systemic chemotherapy may represent the most efficacious approach to the use of drugs with intra-abdominal sarcoma.

We are happy to state that our own clinical trial using cytoreductive surgery and intraperitoneal chemotherapy is underway with sarcomatosis patients. The proper pharmacokinetic studies have been completed. Patients are being treated on a regular basis with standardized drug doses and schedules. Critical clinical evaluation and statistical analysis is regularly employed for this group of patients. Our results in the treatment of approximately 50

patients with sarcomatosis represents a manuscript in preparation. We thank Dr. Neifeld for stimulating us to prepare our report regarding this interesting group of patients who may have new treatment options with the use of cytoreductive surgery and intraperitoneal chemotherapy.

Finally, from the perspective of natural history, this manuscript establishes one important aspect of the pathobiology of extremity sarcoma. These sarcomas can metastasize to peritoneal surfaces and present as sarcomatosis. Dr. Neifeld suggests that the route of dissemination may be extremity sarcoma to lung, and then lung to peritoneal cavity. In two patients, this may have occurred. It makes no difference regarding the reality of the phenomenon. Extremity sarcoma, similar to breast cancer and a number of other malignancies, can metastasize to the peritoneal surfaces. When we evaluated these patients, the sarcomatosis was very symptomatic and required treatment.

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Paul H. Sugarbaker, MD, FACS